The claims have been amended as suggested by the Examiner to more particularly point out and distinctly claim the invention. As requested by the Examiner, an appendix of the claims pending upon entry of this amendment is attached hereto as Exhibit A.

Applicants believe the abstract of the disclosure to be commensurate in scope with the claimed invention and respectfully request that the Examiner clarify the objections to the Abstract.

1. The Rejections Under 35 U.S.C. § 112, First Paragraph, Should be Withdrawn

The specification is objected to and Claims 48 and 49 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. The Examiner maintains that the claims encompass cell lines that are able to support the growth of an adenovirus that is missing the essential genes of the E1, E2A and/or E4 gene regions, but that the structural elements recited are limited to expression cassettes that encode essential E1 and E4 products. The claims have been amended as suggested by the Examiner to recite that the cell lines also comprise the adenoviral E2A region under the control of an inducible promoter. This amendment to the claims is fully supported by the specification and does not constitute new matter (e.g., see instant specification at page 14, lines 9-17). Thus, the Examiner's rejection is obviated by the amendment to the claims, and should be withdrawn.

2. The Rejections Under 35 U.S.C. § 112, Second Paragraph, Should be Withdrawn

Claims 37-39, 46-50, 52, 54, 56 and 57 are rejected under 35 U.S.C.§ 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The claims have been amended as suggested by the Examiner to more particularly point out the invention as claimed, thereby obviating the Examiner's rejection. Thus, the Examiner's rejections under 35 U.S.C. § 112 should be withdrawn.

3. The Rejections Under 35 U.S.C. § 102 Should Be with Withdrawn

Claims 37, 38, 46, 47, 52, 54 and 56 drawn to a replication-defective recombinant adenovirus are rejected under 35 U.S.C. §102 as anticipated by Gregory et al. U.S. Patent No. 5,670,888 ("Gregory").

The Examiner contends that Gregory describes PAVs in which the only adenoviral sequences present are the inverted terminal repeats (ITRs) and packaging sequence and a transgene replaces the deleted E1, E2A, E3 and E4 regions. Thus, the Examiner concludes that Gregory anticipates the recombinant adenoviruses and vectors of the present invention which require lethal deletions of E1 and E4 gene regions. This rejection is in error for the reasons explained below.

The legal test for anticipation under 35 U.S.C. § 102 requires that each and every element of the claimed invention be disclosed in a prior art reference in a manner sufficient to enable one skilled in the art to reduce the invention to practice, thus placing the public in possession of the invention. W.L. Gore Associates v. Galock, Inc., 721 F.2d

1540, 1554 (Fed. Cir. 1983) cert. denied 469 U.S. 857 (1984); In re Donohue, 766 F.2d 351 (Fed. Cir. 1985). Anticipation under 35 U.S.C. § 102 requires identity of invention. Scripps Clinic & Research Fdn. v. Genentech Inc., 927 F.2d 1565 (Fed. Cir. 1991). Anticipation under 35 U.S.C. §102 also requires that the prior art reference places the claimed invention in the possession of the public through an enabling disclosure. Charles v. Miller, 906 F.2d 1574, 15 USPQ 2d 133 (Fed. Cir. 1990).

Gregory does not anticipate the recombinant adenoviruses and vectors of the present invention which contain lethal deletions in the E1A and E4 early gene regions and require complementation with E1A and E4 gene regions for rescue. The only packaged adenoviral vector described in Gregory is one which must retain the essential region of E4, ORF6, so that complementation with E4 is not required to achieve rescue of the adenoviral vector. Gregory does not teach and enable the production and use of adenoviruses with deletions of the essential regions of E1 and E4, because it was not known how to provide both of these functions in a "non-suicidal" packaging cell line. This problem plagues the other constructs described in Gregory as well, in particular the PAVs, as Gregory does not accomplish nor enable rescue of an adenoviral vector carrying a lethal deletion of the E4 early gene region. In fact a close inspection of the working examples of Gregory reveals that rescue of the PAVs is described in the present tense, thus it is clear that rescue was not achieved, and further, given Gregory's teaching it is doubtful that rescue could actually be accomplished. Thus,

these vectors do not anticipate the recombinant adenoviruses of the present invention.

In this instance, the present invention defined by the claims cover replication-defective recombinant adenoviruses containing at least two lethal deletions in the E1, E2A or E4 early gene regions. The deletion of two essential regions, e.g., both the E1 and E4 regions, dramatically minimizes or eliminates the pathogenic effects of direct cytotoxicity to the targeted cells and inflammatory responses in the human body. The resulting virus, however, is replication-defective and requires the E1 and E4 functions in trans in order to replicate.

Prior to the present invention, it was not possible to generate a recombinant adenovirus containing lethal deletions in all of the essential regions of the E1, E2A and E4 gene regions. This is due to the fact that once the DNA encoding the adenoviral genome had been manipulated to contain these deletions, there was no way to provide the toxic gene products encoded by the E1, E2A and E4 gene regions in trans in order to rescue a packaged recombinant adenovirus. It was the present invention which provided the methods and the packaging cell line which allows the generation and rescue of a recombinant adenovirus containing lethal deletions of the E1, E2A and E4 early gene regions.

Gregory also recognizes the problem of the toxicity of many of the essential adenoviral gene products, and attempts to generate second-generation vectors containing minimal adenoviral regulatory, packaging and replication sequences in order to minimize the cytotoxicity of the adenoviral vectors.

However, Gregory does not solve the problem of how to supply the essential toxic gene products in trans, in particular the E4 early gene products. Thus, Gregory does not describe a method of successfully supplying the E4 functions in trans which is necessary to rescue an adenoviral genome containing a lethal deletion or mutation in the E4 early gene region. Rather, Gregory describes a recombinant adenovirus packaged from an adenoviral genome containing a deletion in all of the E4 open reading frames, however, leaving intact the essential E4 open reading frame 6 (ORF6) in order to maintain E4 functions in the virus. However, these deletions of non-essential regions as described in Gregory do not constitute the lethal deletions of E1 and E4 in the replication defective recombinant adenoviruses of the present invention. It is telling that the only packaged adenoviral vector described in Gregory is one in which all the non-essential regions of E4 have been deleted, but the essential ORF6 is maintained, bypassing the need to provide E4 in trans. Thus, the problem of providing E4 in trans remains unsolved by Gregory. In fact, the adenoviral vectors as claimed by Gregory require that sufficient E4 sequences are maintained within the viral vectors to promote virus replication.

In summary, Gregory does not describe a recombinant adenovirus, or the rescue of an adenoviral vector, which contains lethal deletions in the E1, E2A and E4 early gene regions, because it was simply not known how to successfully supply the E1, E2A and E4 early gene products in trans without killing the packaging cell line. It is the instant invention that provides recombinant adenoviruses and vectors containing

these lethal mutations, that are successfully rescued and packaged by complementation with E1, E2, and E4 in trans.

Thus, the recombinant adenoviruses and vectors of the present invention are not anticipated by the cited art and, therefore, the Examiner's rejections under 35 U.S.C. § 102 should be withdrawn.

CONCLUSION

Applicants respectfully request entry and consideration of the foregoing amendments and remarks. Applicants believe the claims to be in condition for allowance.

Respectfully submitted,

by

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Enclosure

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